Investor Update

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New Study Suggests that Xenical (orlistat) has Benefits Beyond Weight Loss for Insulin-Dependent Type 2 Diabetes Patients

Improvements in glycemic control and cardiovascular risk factors were also observed; Need for insulin and oral diabetes medications reduced

Treatment with the prescription weight-loss medication Xenical (orlistat) can have significant benefits for overweight or obese people with insulin-treated type 2 diabetes who have sub-optimal metabolic control, according to a new study published in the June issue of the journal Diabetes Care. Treatment benefits were seen in body weight, glycemic (blood glucose) control, serum cholesterol and LDL/HDL ratio (good/bad cholesterol). This is the first study to explore the effects of Xenical treatment in overweight or obese insulin-dependent type 2 diabetes patients.

"Glycemic control is the goal of diabetes treatment and weight loss plays a key role in maintaining glycemic control," said David E. Kelley, M.D., director of the University of Pittsburgh Obesity & Nutrition Research Center and lead investigator in the study. "These results demonstrate that the addition of orlistat to the treatment regimen that includes diet and insulin produce better glycemic control than diet therapy alone in this patient population. This is a significant finding that could have implications on how these patients are treated in the future."

More than 80% of people with type 2 diabetes are obese, and weight loss is especially challenging for insulin-treated type 2 diabetes patients because insulin therapy has been found to cause weight gain. Being overweight also makes it more difficult to control blood glucose and increases the chances of cardiovascular complications in diabetes patients.

About the Study

A total of 535 patients (56% female/44% male) at 43 sites in the United States participated in the

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double-blind study. Subjects were randomised to receive either insulin and Xenical 120 mg three times a day plus diet (n = 274) or insulin plus placebo plus diet (n = 276). The diet was reduced in calories, consistent with the ADA dietary recommendations. At enrollment, the two groups were similar in terms of gender, race, body weight, mean daily insulin dose, serum HbA_{1c}, fasting glucose and use of oral diabetes medications. Fifty-one percent of the Xenical group (137) and 47% of the placebo group (128) completed 52 weeks of treatment.

At the end of the study, participants treated with Xenical experienced greater weight loss compared to patients receiving placebo (-3.76% of baseline body weight vs. –1.22%). In addition, more patients treated with Xenical lost 5% or more of their body weight (33% vs. 13%). And in the Xenical group, three times more patients achieved a 10% weight loss compared to the placebo group.

Patients in the Xenical group also had, on average, twice as great a reduction in serum HbA_{1c} levels at the study's conclusion compared to the placebo group (–0.62% vs. –0.27%). More over, the improvement in HbA_{1c} was –1.0% for patients on Xenical plus insulin plus diet and –0.57% for patients on placebo plus insulin plus diet in individuals whose value for HbA_{1c} was equal to or greater than 9% before treatment was begun. Notably, the greater reduction in HbA_{1c} seen with Xenical treatment was not entirely dependent on weight loss. After adjusting for differences in weight loss, the mean change in HbA_{1c} remained significantly different between groups (–0.56% vs. –0.32% for the Xenical and placebo treatment groups, respectively).

Xenical therapy was also associated with a reduced need for insulin and oral diabetes medicines. On average, Xenical patients saw a significant reduction in daily insulin dose when compared to the placebo treated group (-8.1 units per day reduction for the Xenical group vs. -1.6 units per day reduction for the placebo group). More Xenical-treated patients (41.3%) decreased or discontinued at least one oral diabetes medication during the study compared to placebo (30.9%).

At 52 weeks, Xenical-treated patients had greater improvements in total cholesterol, LDL-cholesterol, and ratio of LDL to high-density lipoprotein (HDL) – or good – cholesterol than placebo-treated patients. However, changes in serum triglycerides and HDL-concentration did not differ significantly between the treatment groups.

Overall, 54% of placebo-treated and 50% of Xenical-treated patients withdrew prematurely from the study. Thirteen percent of Xenical-treated patients discontinued treatment because of a

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gastrointestinal-related adverse event, compared to 8% in the placebo group. Except for a greater frequency of hypoglycemia (low blood sugar) in the Xenical-treated group, the incidence of adverse events not related to the gastrointestinal system was similar in both study arms.

About Type 2 Diabetes

Type 2 diabetes is a disorder that causes too much sugar to circulate in the blood. It can lead to heart disease, stroke, high blood pressure, blindness, kidney disease, nervous system damage, and amputation. If fact, people with diabetes are two to four times more likely to have heart disease, and three quarters of all people with diabetes will die from heart disease. Obesity is a major risk factor for developing type 2 diabetes and insulin resistance.

An estimated 15.7 million adults in the U.S. have diabetes, with type 2 diabetes accounting for about 90 to 95 percent of these cases. A study conducted by the Centers for Disease Control and Prevention (CDC) found that the incident of type 2 diabetes among adults has increased rapidly throughout the 1990s across all regions and demographic groups. In addition, the prevalence of obesity has increased 57 percent in the last decade, suggesting that further increases in the prevalence of type 2 diabetes can be expected.

About Xenical

Approved in April 1999 for weight loss, maintenance of lost weight, and the reduction of risk of weight regain after prior weight loss when used with a reduced-calorie diet, Xenical is the only non-systemically acting gastrointestinal lipase inhibitor. Its mechanism of action is to prevent one-third of dietary fat from being absorbed.

Weight loss with Xenical also has resulted in improvements in many cardiovascular risk factors such as high blood pressure, high cholesterol, and diabetes, compared with diet alone. Xenical has an established safety profile and is the most extensively studied weight management treatment to date. Xenical has been used in two million patients worldwide. The long-term effects of Xenical on morbidity and mortality associated with obesity have not been established.

Xenical patients are eligible to participate in XENICare, a comprehensive weight-loss support program. Those participating in the program receive personal telephone counseling from a registered nurse or dietitian specially trained to provide weight-loss support. In addition, patients may receive ongoing information and resources designed to maximize their success.
Because Xenical prevents about one-third of the fat in the food consumed from being absorbed,

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patients may experience gas with oily discharge, increased bowel movements, an urgent need to have them and an inability to control them, particularly after meals containing more fat than recommended. In clinical trials, these effects appear to occur less often among Xenical patients with type 2 diabetes than in patients treated for obesity.

Xenical should not be taken if patients are pregnant, nursing, have food absorption problems or reduced bile flow. If taking cyclosporine, patients should speak to their doctors before taking Xenical. Xenical reduces the absorption of some vitamins. Therefore, a daily multivitamin is recommended.

About Roche

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